initial diagnoses included ASD (28%), Chiari malformation (21.8%), developmental disorders (15.6%), epilepsy (15.6%), and ADHD (12.5%). Slightly over one third of respondents (37.5%) reported a diagnosis of Pierport Syndrome. Of those diagnosed with Pierport Syndrome, the majority reported characteristic dysmorphic features. In contrast to the prior literature linking Pierport Syndrome to a limited number of missense variants in TBL1X/R1, survey respondents reported this diagnosis linked with a wider array of genetic variants including novel missense variants, frameshifts, and copy number variants (CNV).

Time of acquisition of early developmental milestones was obtained, and a wide spectrum of development was seen. Developmental regression was seen in a minority of respondents, with 15.6% reporting motor regression, 21.8% with language regression, and 9.3% with social regression. As epilepsy is one known cause of developmental regression, the relationship between seizures and developmental regression was examined. Nine respondents (28.1%) reported experiencing seizures at any point. Over half of those with seizures also endorsed language regression. The relationship between seizures and motor or social regression was less apparent, with two patients with epilepsy reporting gross motor regression and one reporting social regression. Notably, although the majority of respondents indicated that their seizures were currently controlled, the most recent seizure had occurred in the past two years in all patients for whom that data was available (one patient did not provide a current age, and one did not provide the age at the time of seizures). Reported seizure types included absence, focal, and tonic, and there was no relationship between seizure type and the presence of regression.

Twenty-five respondents provided their genetic information. Of these, 24 reported novel variants not found in the prior literature, including duplications leading to frameshifts, in-frame deletions, missense variants, intronic point variants, and CNVs. Of the missense variants and in-frame deletions, all were found exclusively within the WD40 regions that are felt to be responsible for protein-protein binding.

**Conclusion:** The 32 completed surveys analyzed in this study represent the largest cohort of patients with TBL1X/R1-related disorder to date. The data reveals a disorder characteristic by delayed development ranging in severity, with a subset of patients experiencing developmental regression. Interestingly, seizures were found to be associated primarily with language regression rather than regression in other developmental domains. There was no clear association between seizure type and the presence of regression. The interplay between seizures and developmental regression in this population is not fully explained and remains an area for future exploration.

https://doi.org/10.1016/j.gim.2022.01.232

---

### e197

**Further delineation of KIF21B-related neurodevelopmental disorders**

Dhanya Lakshmi Narayanan\(^1\), Michelle Rosario\(^2\), Vivekananda Bhat\(^1\), José Rivera Alvarez\(^3\), Juliette Godin\(^1\), Anju Shukla\(^2\)

\(^1\)Department of Medical Genetics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India, DBT/Wellcome Trust India Early Career Fellow; \(^2\)Department of Medical Genetics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India; \(^3\)Institut de Génétique et de Biologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique, Institut National de la Santé et de la Recherche Médicale, Université de Strasbourg

**Background:** KIF21B (Kinesin Family Member 21B) encoded by KIF21B (MIM*608322), belongs to the Kinesin Superfamily proteins, which play a key role in microtubular organisation in neuronal dendrites and axons. KIF21B regulates microtubule network dynamics and promotes intracellular anterograde transport in neurons. Homozygous knock out mice were shown to have microcephaly, altered synaptic transmission, cognitive defects and reduced dendritic complexity, implicating the role of KIF21B in brain function. Recently, four unrelated individuals with developmental delay, intellectual disability, non-specific facial dysmorphism and corpus callosal agenesis were described with heterozygous variants in KIF21B. Three of the variants were missense variants and one was a frameshift variant. In vivo modelling showed that KIF21B variants affected neuronal migration due to impairment of kinesin motor activity. KIF21B was thus implicated as a novel candidate gene for intellectual disability and brain malformations.

**Case presentation:** A nine-year-old male, firstborn of non-consanguineous parents, was evaluated for delayed speech, hyperactivity and poor social interaction. After an uneventful antenatal period, he was born at term with a birth weight of 2.8kg (-0.4SD). He cried immediately after birth and had an uncomplicated neonatal course. He had a delay in attaining age-appropriate milestones. He could stand without support only by 1 year and 4 months of age. He started babbling by 9 months of age and could say bisyllables by 4 years of age. He had poor eye contact and did not respond to his name. At 2 years of age, he developed hyperactivity, low attention span and was unable to play with other children. At 3 years, Vineland Social Maturity Scale showed a score of 81, indicating a dull normal level of social and adaptive functioning. The Modified Checklist for Autism in Toddlers Score at 3 years was 3, indicating a moderate risk for autism spectrum disorder. There was no history of seizures or motor deficit. Currently, at 9 years of age, he is able to jump, say a few words and write single words. He needs assistance in grooming and showering. He attends sessions with a special educator. He is on atomoxetine and risperidone and parents perceive improvement in his hyperactivity. On examination, his weight is 24.8kg (+0.8SD), height is 133cm (+0.5SD) and head circumference is 53cm (0 SD). He has a long face, broad eyebrows, multiple lentigines on face and back and bilateral fifth digit clinodactyly. Brain Evoked Response Audiometry was normal. Magnetic Resonance Imaging of brain did not show any major structural malformation.

**Genetic testing:** Fragile X screening did not show any repeat expansion. Chromosomal microarray analysis did not reveal any clinically relevant variants. A parent-offspring trio exome sequencing showed a de novo heterozygous variant, NM_001252102.2: c.1513A>C, p.(Ser505Arg) in exon 11 of KIF21B. Sanger sequencing confirmed this variant. The variant was absent in population databases like gnomAD and our in-house database of 1143 individuals. Multiple in silico analysis tools like MutationTaster, Clinpred and CADD predicted the variant to be disease-causing. The variant was classified as a variant of uncertain significance based on the standards and guidelines for interpretation of sequence variants by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

**In silico protein modelling and analysis**

The protein structure of KIF21B was obtained from AlphaFold Protein Structure Database (AF-O75037-F1), loaded on PyMol (The PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC) and in silico mutagenesis was performed to deduce the structure of the mutant protein. 3D protein modelling was done to analyse the alteration in polar contacts of the wild-type residue of interest (Ser505) with its neighbouring amino acids as compared to the mutant residue (Arg505). The mutant residue was predicted to cause abrogation of one of two polar contacts with the wild-type residue (Ser501). The structural effect of the missense substitution Ser505Arg was also predicted using HOPE (http://www.cmbi.ru.nl/hope/). HOPE predicted the impact of the wild type and mutant residues at the 505 position with regards to their charge, size and hydrophobicity. The wild-type residue (Ser505) was predicted to introduce a positive charge, thus causing repulsion of ligands or other residues with the same charge. Also, the replacement of the wild-type (smaller) residue with the mutant (bigger) amino acid was predicted to lead to collisions. The variant introduced a less hydrophobic residue, resulting in the probable loss of hydrophobic interactions in the core or
surface of the protein. Additionally, HOPE predicted that the variant was located within a stretch of residues, which interacted with TRIM3, and thus the differences in amino acid properties caused by the mutant could result in disturbance of the function of this region.

**Conclusion:** We describe a novel de novo variant in KIF21B in a nine-year-old male with developmental delay, autism spectrum disorder and hyperactivity, providing further evidence to the gene-disease association. Our report expands the genotype and phenotype of KIF21B-related neurodevelopmental disorders.

https://doi.org/10.1016/j.gim.2022.01.233

### eP198

**EIF3F compound heterozygous genotype-phenotype association**

Elena-Raluca Nicoli1, Ioana Streata2, John Yang3, Ellen Macnamara1, Lynne Wolfe1, Karolyn Garcia1, Tudorel Ciurea2, Mihai Ioan2, William Gahl4, Cynthia Tifft5, Maria Acosta3, David Adams3

1Glycosphingolipid and Glycoprotein Disorders Unit, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD; 2University of Medicine and Pharmacy of Craiova; County Clinical Emergency Hospital Craiova, Romania; 3Undiagnosed Diseases Program, The Common Fund, NIH, Bethesda, MD; 4Human Biochemical Genetics Section, MGB, NHGRI; 5Undiagnosed Diseases Program Program, The Common Fund; Office of the Clinical Director, NHGRI, NIH, Bethesda

**Background:** Phenotypes for newly described gene-disease associations often undergo rapid evolution as additional cases are described. The expansion of exome and genome sequencing has contributed to this phenomenon by allowing ascertainment of diseases based on genotype rather than phenotype. We describe an example of phenotype expansion for the EIF3F gene, which encodes an essential subunit of the mammalian eukaryotic initiation factor (eIF2B) complex. EIF2F is important for translation regulation and is involved in cell proliferation and growth, cell cycle control, differentiation, and apoptosis. EIF3F gene has been implicated in severe autosomal recessive neurodegenerative disorders, including the disorder “Mental retardation, autosomal recessive 67” (OMIM #618295), which includes cognitive impairment, hearing loss and seizures. We describe a newly diagnosed case with white matter changes not previously associated with the disorder.

**Case presentation:** The proband is a 4 year- and 11 month-old Romanian boy born to healthy, non-consanguineous parents. There was no family history of known congenital anomalies, genetic disorders, epilepsy, or intellectual disability. A 12-week ultrasound identified increased nuchal translucency (3.8 mm). Amniocentesis was performed at 16 weeks; QF-PCR and karyotype revealed normal results. Subsequent ultrasound evaluations yielded normal results. Decreased fetal movement was noted. Apgar scores were 9 at both 1- and 5-min. Birth weight was 3,200 g (10th centile), length was 50 cm (25th centile), and occipital frontal diameter (OFD) was 33cm (45th centile). Physical examination revealed muscular hypotonia, hypospadias, and 2,3-foot syndactyly. Newborn hearing screening was abnormal. Congenital visual impairment with nystagmus and convergent strabismus were present. Extensive metabolic screening and an electroencephalogram (EEG) study performed during the neonatal period were normal. During the first months of life, the patient showed severe hypotonia, global developmental delay (motor, cognitive and speech), muscular hypotonia, dysmorphic facial features (skin and hair hypopigmentation, micrognathia, and hand brachydactyly). Hearing assessment at the age of 6 months identified mild bilateral neuro-sensory hearing loss with a 60 dB threshold (ABR test with anesthesia). At the age of 9 months, a 1.5T brain MRI revealed extensive supratentorial leukodystrophy. Genomic evaluation included a CGH high resolution micro array (aCGH), exome sequencing and genome sequencing. The aCGH study detected a region of absent heterozygosity in 2q11.1q11.2. Exome and genome sequencing were initially negative, but detected two heterozygous variants in the EIF3F gene on reanalysis of the genome 36 months after the initial interpretation. Clinical features reported to be associated with EIF3F gene variants include intellectual disability, epilepsy, behavioral problems, sensorineural hearing loss, congenital anomalies (left lip and palate, congenital lobar emphysema, anal stenosis, and undescended testis), neurological symptoms and non-specific brain MRI changes. Similar findings were identified in our patient, with the addition of white matter changes.

**Conclusion:** Our paper provides a detailed clinical presentation of boy affected with autosomal recessive Mental retardation type 67 (MRT67, OMIM 618295) and expands the mutational spectrum associated with this extremely rare genetic condition. This is the first case of MRT67 identified in Romania.

https://doi.org/10.1016/j.gim.2022.01.234

### eP200

**Noonan syndrome associated with focal occipital alopecia in a patient with RAF1 variant: A case report and literature review**

Elizabeth Null1, Ann Haskins Olney1, Andria Powers2

1Munroe-Meyer Institute for Genetics and Rehabilitation, Omaha, NE; 2Department of Radiology, Children's Hospital and Medical Center, Omaha, NE

**Background:** Noonan syndrome (NS) is a heterogenous condition characterized by distinctive craniofacial features, cardiac defects, and neurodevelopmental changes and is caused by variants in one of seven genes coding for proteins within the Ras-MAPK pathway. Pathogenic variants in RAF1 account for approximately 3-17% of cases and are associated with a high prevalence of severe hypertrophic cardiomyopathy (HCM) and pulmonary hypertension (PHTN). Cerbrovascular and Chiari I malformations, although rare, have also been described in individuals with RAF1 NS. To our knowledge, the presence of congenital occipital alopecia in an individual with NS has not been previously reported.

**Case presentation:** We report a patient with a de novo pathogenic heterozygous RAF1 gene sequence variant, c.770C>T (p.Ser257Leu), with atypical scalp findings. Our proband was a 4-year-old female dichorionic, diamniotic twin born at 35 weeks 2 days gestation to nonconsanguineous parents. At birth, her length was 45.7 cm (14th centile), weight was 2656 g (69th centile), and head circumference was 34.5 cm (97th centile). The mother was 38 at the time of birth. There was no history of maternal or gestational diabetes. Prenatal ultrasound was concerning for cystic hygroma. The immediate neonatal course was uneventful. Birth weight was 3,200 g (10th centile), length was 50 cm (25th centile), and weight was 2656 g (69th centile). The mother was 38 at the time of birth. The proband is a 4 year- and 11 month-old Romanian boy born to healthy, non-consanguineous parents. There was no family history of known congenital anomalies, genetic disorders, epilepsy, or intellectual disability. A 12-week ultrasound identified increased nuchal translucency (3.8 mm). Amniocentesis was performed at 16 weeks; QF-PCR and karyotype revealed normal results. Subsequent ultrasound evaluations yielded normal results. Decreased fetal movement was noted. Apgar scores were 9 at both 1- and 5-min. Birth weight was 3,200 g (10th centile), length was 50 cm (25th centile), and occipital frontal diameter (OFD) was 33cm (45th centile). Physical examination revealed muscular hypotonia, hypospadias, and 2,3-foot syndactyly. Newborn hearing screening was abnormal. Congenital visual impairment with nystagmus and convergent strabismus were present. Extensive metabolic screening and an electroencephalogram (EEG) study performed during the neonatal period were normal. During the first months of life, the patient showed severe hypotonia, global developmental delay (motor, cognitive and speech), muscular hypotonia, dysmorphic facial features (skin and hair hypopigmentation, micrognathia, and hand brachydactyly). Hearing assessment at the age of 6 months identified mild bilateral neuro-sensory hearing loss with a 60 dB threshold (ABR test with anesthesia). At the age of 9 months, a 1.5T brain MRI revealed extensive supratentorial leukodystrophy. Genomic evaluation included a CGH high resolution micro array (aCGH), exome sequencing and genome sequencing. The aCGH study detected a region of absent heterozygosity in 2q11.1q11.2. Exome and genome sequencing were initially negative, but detected two heterozygous variants in the EIF3F gene on reanalysis of the genome 36 months after the initial interpretation. Clinical features reported to be associated with EIF3F gene variants include intellectual disability, epilepsy, behavioral problems, sensorineural hearing loss, congenital anomalies (left lip and palate, congenital lobar emphysema, anal stenosis, and undescended testis), neurological symptoms and non-specific brain MRI changes. Similar findings were identified in our patient, with the addition of white matter changes.

**Conclusion:** Our paper provides a detailed clinical presentation of boy affected with autosomal recessive Mental retardation type 67 (MRT67, OMIM 618295) and expands the mutational spectrum associated with this extremely rare genetic condition. This is the first case of MRT67 identified in Romania.

https://doi.org/10.1016/j.gim.2022.01.234